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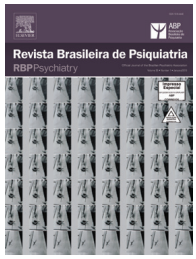

SPECIAL ARTICLE

Staging and neuroprogression in bipolar disorder: a systematic review of the literature

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Abstract

Introduction: The use of clinical staging models is emerging as a novel and useful paradigm for diagnosing severe mental disorders. The term "neuroprogression" has been used to define the pathological reorganization of the central nervous system along the course of severe mental disorders. In bipolar disorder (BD), neural substrate reactivity is changed by repeated mood episodes, promoting a brain rewiring that leads to an increased vulnerability to life stress. *Method:* A search in the PubMed database was performed with the following terms: "staging", "neuroprogression", "serum", "plasma", "blood", "neuroimaging", "PET scan", "fMRI", "neurotrophins", "inflammatory markers" and "oxidative stress markers", which were individually crossed with "cognition", "functionality", "response to treatments" and "bipolar disorder". The inclusion criteria comprised original papers in the English language. Abstracts from scientific meetings were not included. *Results:* We divided the results according to the available evidence of serum biomarkers as potential mediators of neuroprogression, with brain imaging, cognition, functioning and response to treatments considered as consequences. *Conclusion:* The challenge in BD treatment is translating the knowledge of neuronal plasticity and neurobiology into clinical practice. Neuroprogression and staging can have important clinical implications, given that early and late stages of the disorder appear to present different biological features and therefore may require different treatment strategies.

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Introduction

The use of clinical staging models is emerging as a novel and useful paradigm for diagnosing severe mental disorders.[1] The staging concept is particularly practical, as it can differentiate early, milder clinical phenomena from those that accompany illness progression and chronicity.[2] The logic of staging is based on accessing the clinical features of a patient within a longitudinal perspective of illness development to provide different treatment approaches according to their specific pathophysiological, symptomatic and structural changes at each stage of illness.[3]

The term "neuroprogression" has been increasingly used to define the pathological reorganization of the central nervous system (CNS) along the course of severe mental disorders.[4] This reorganization could arise as the result of several insults, such as inflammation and oxidative stress.[5] In bipolar disorder (BD), neural substrate reactivity is changed by repeated mood episodes, ultimately promoting a brain rewiring that leads to an increased vulnerability to life stress.[6-8]

Recurrent episodes influence the outcome of BD by increasing a patient's vulnerability to subsequent episodes and reducing the treatment response.[9] An episode-dependent deterioration pattern has been widely described in serum biomarkers,[4,10] brain imaging[11,12] and functioning.[13-16] Therefore, staging models emphasizing the assessment of patients in the interepisodic period[17-20] have been proposed to personalize and optimize treatments for BD.[21]

The neurobiological mechanisms of more pronounced neuroanatomical brain changes in patients with multiple mood episodes of BD appear to include increased oxidative stress, increased pro-inflammatory markers and a deficit in neuroprotection.[4] Although definitive empirical evidence is lacking, staging and neuroprogression can be conceived of as two facets of the same phenomenon (Figure 1).[22]

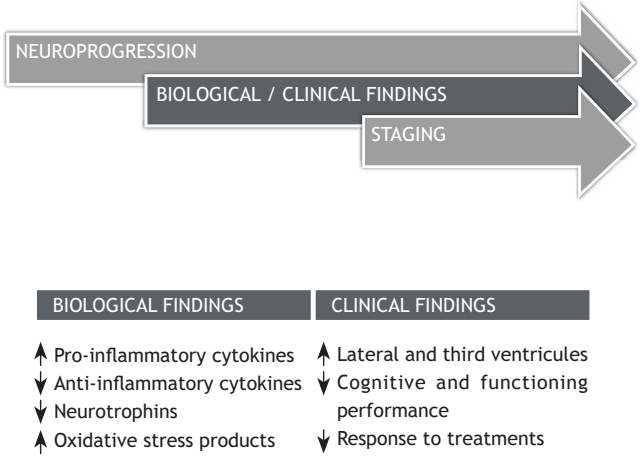

Figure 1 Linking neurobiological and clinical findings to neuroprogression and staging.

Methods

A search in the PubMed database was performed with the following terms: "staging", "neuroprogression", "serum", "plasma", "blood", "neuroimaging", "PET scan", "fMRI", "neurotrophins", "inflammatory markers" and "oxidative stress markers", which were individually crossed with "cognition", "functionality", "response to treatments" and "bipolar disorder" (BD).

The inclusion criteria comprised original papers in the English language. Abstracts from scientific meetings were not included. There was no limit for the year of publication, and the search included papers until July 2012.

The search retrieved 70 articles, from which 65 were included. The remaining 5 articles were excluded for the following reasons: case report (n = 2), comment on an original paper (n = 1) and studies focusing on other disorders and conditions (n = 2).

Results

We divided the results according to available evidence of serum biomarkers as potential mediators of neuroprogression, with brain imaging, cognition, functioning and response to treatments considered as consequences.

Serum biomarkers

Data from different lines of research converged to the brain-derived neurotrophic factor (BDNF) as an important contributor to neuroplastic changes in BD. Serum BDNF levels have been shown to be decreased during depressive and manic episodes and to return to normal levels in euthymia.[23-26] In this line, a decrease in BDNF levels acts as a state-dependent biomarker for mood episodes in BD.[27,28] It has also been shown that decreased BDNF levels are found in chronic or late-stage individuals with BD, in comparison to patients in early stages of the illness,[29] and an overall accelerated age-related decrease of BDNF was discovered in patients with BD.[30] In young adults with bipolar disorder recruited from the general population, BDNF levels tend to be similar to those of healthy controls.[22]

Factors that negatively influence the course of BD, such as life stress and trauma, have been shown to be associated with a decrease in serum BDNF levels among people with bipolar disorder.[31] However, effective treatments, such as lithium and divalproex, have proven to prevent cellular atrophy, to have anti-apoptotic properties and to increase BDNF levels.[32]

Available evidence indicates that BD and inflammation are linked through shared genetic polymorphisms and gene expression, as well as altered cytokine levels[33] during acute episodes[34,35] and euthymia.[36,37] It has been suggested that inflammatory cytokines, particularly TNF-α, may play a critical role in the process of changes in neuroplasticity, cell resilience and neuronal survival.[38,39] Additionally, BDNF and TNF-α serum levels combined have been proposed as staging biomarkers for BD.[17] When early- and late-stage patients with BD were compared, IL-6 and TNF-α were elevated in both groups, while IL-10 levels were higher in the early stages. However, TNF-α was higher in late stages than in early.

BD is associated with an imbalance in oxidative biology and often involves an increase in lipid damage that is measured by thiobarbituric reactive substances (TBARS) and

nitric oxide (NO) and a decrease in antioxidant enzymes, such as superoxide dismutase (SOD).[40] TBARS serum levels are increased, regardless of mood state,[41] and are more pronounced in mania. Inversely, protein damage was higher in depression than in mania in one study.[42] An increase in protein damage was also found in young people with early-stage bipolar disorder and may be an early indication of systemic toxicity.[43] Apart from protein carbonylation, there is an increased frequency of DNA damage in patients with BD when compared to controls; this damage is correlated to severity of depression and manic symptoms.[44] Furthermore, both depressed and euthymic bipolar patients present endothelial function impairment due to oxidative stress that may contribute to increase their risk for cardiovascular conditions.[45] A negative correlation between BDNF and TBARS was found in a BD cohort during manic episodes.[46] Hence, oxidative stress may also help to link the accelerated aging, cognitive and functional impairment and premature mortality observed in BD.[47]

Due to the important role of neurotrophins, oxidative stress markers and inflammatory markers in BD, a systemic toxicity index was proposed to assess peripheral changes in mood episodes. These systemic markers were shown to differentiate between acute mood states and two control conditions, healthy adults and people with sepsis, with the acute mood states positioned as intermediaries between the two controls.[42,48] As an aggregate, these biological markers were subtly elevated in people from the general population in early stages.[49] Further study is needed to demonstrate how this systemic toxicity differs in early- and late-stage bipolar disorder.

Brain imaging, cognition, functioning and response to treatments

Alterations in brain structures have been widely reported in BD patients. Morphometric studies have demonstrated that patients with BD show an enlargement of the third and lateral ventricles; a reduction in the gray matter volumes of the orbital and medial prefrontal cortex, ventral striatum and mesotemporal cortex; and an increase in the size of the amygdala.[12,50-52] Such neuroanatomical changes tend to be more pronounced in patients with repeated episodes.[11,12] In terms of neuropathological findings, recent data suggest that changes in neuroplasticity, particularly in cell resilience and connectivity, are the main findings in BD.[52]

Patients with bipolar disorder present cognitive impairment during both the acute phase of illness and remission, which seems to worsen with cumulative episodes.[53-56] The main cognitive impairment has been demonstrated to affect executive functions, while moderate cognitive deficits was observed in other cognitive tests, such as verbal memory, response inhibition, sustained attention, psychomotor speed, abstraction and set-shifting.[57] Deficits in executive function and verbal memory suggest the impairment of the prefrontal and medial temporal cortices, respectively. Some measures of frontal executive function (Stroop Color Test and Word Test, the Wisconsin Card Sorting Test, the FAS subtest, and the digit subtest backward) and of learning and memory tasks (Wechsler Memory Scale - Revised and the California Verbal Learning Test) have been found to be associated with poorer functional outcomes. Difficulties in remembering long-term information are associated with lower occupational functioning in BD,[58,59] and poor cognitive functioning is one of the main factors that explains the high rates of disability and burden associated with BD.[60] In addition to these, psychosocial functioning impairment presents a progression[13,14] and is present during euthymia.[61]

Illness progression is also associated with changes in treatment response. The response to lithium is inversely correlated to the number of episodes[62] and duration of illness prior to starting treatment.[63] Consistently, olanzapine was found to be more effective early in the course of BD.[9] The same findings were replicated in the field of psychosocial treatments where patients with multiple recurrences do not seem to respond to adjunctive cognitive behavioral therapy[16] or to family psychoeducation.[15] Recently, an analysis of the STEP-BD dataset replicated a meta-analysis that revealed that people with more than 10 previous episodes have an overall worse treatment response, which was stable during follow-up.[64]

Conclusion

Acute mood episodes have been associated with significant systemic toxicity, cognitive and functional impairment and biological changes.[42,49] These effects are cumulative and are much more prominent after multiple episodes.[29,50,66,67] It is plausible that mood episodes function as allostatic states, generating a load that accumulates to compromise regulatory systems and ultimately bearing responsibility for the progression of the illness.[6,7]

The challenge in BD treatment is translating the knowledge of the neuronal plasticity and neurobiology of the illness into clinical practice. Neuroprogression and staging can have important clinical implications, given that the early and late stages of the disorder appear to present different biological features and therefore may require different treatment strategies.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

References

1. Wood SJ, Yung AR, McGorry PD, Pantelis C. Neuroimaging and treatment evidence for clinical staging in psychotic disorders: from the at-risk mental state to chronic schizophrenia. Biol Psychiatry. 2011;70(7):619-25.
2. McGorry PD, Nelson B, Goldstone S, Yung AR. Clinical staging: a heuristic and practical strategy for new research and better health and social outcomes for psychotic and related mood disorders. Can J Psychiatry. 2010;55(8):486-97.
3. Francey SM, Nelson B, Thompson A, Parker AG, Kerr M, Macneil C, et al. Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention. Schizophr Res. 2010;119(1-3):1-10.
4. Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, Maes M, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. Neurosci Biobehav Rev. 2011;35(3):804-17.
5. Berk M, Conus P, Kapczinski F, Andreazza AC, Yücel M, Wood SJ, et al. From neuroprogression to neuroprotection: implications for clinical care. Med J Aust. 2010;193(4 Suppl):S36-40.
6. Kapczinski F, Vieta E, Andreazza AC, Frey BN, Gomes FA, Tramontina J, et al. Allostatic load in bipolar disorder: implications for pathophysiology and treatment. Neurosci Biobehav Rev. 2008;32(4):675-92.
7. Vieta E, Popovic D, Rosa AR, Solé B, Grande I, Frey BN, et al. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur Psychiatry. 2012.
8. Grande I, Magalhaes PV, Kunz M, Vieta E, Kapczinski F. Mediators of allostasis and systemic toxicity in bipolar disorder. Physiol Behav. 2012;106(1):46-50.
9. Ketter TA, Houston JP, Adams DH, Risser RC, Meyers AL, Williamson DJ, et al. Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. J Clin Psychiatry. 2006;67(1):95-101.
10. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol. 2009;12(4):447-58.
11. Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry. 2002;159(11):1841-7.
12. Lisy ME, Jarvis KB, DelBello MP, Mills NP, Weber WA, Fleck D, et al. Progressive neurostructural changes in adolescent and adult patients with bipolar disorder. Bipolar Disord. 2011;13(4):396-405.
13. Rosa AR, Gonzalez-Ortega I, Gonzalez-Pinto A, Echeburua E, Comes M, Martinez-Aran A, et al. One-year psychosocial functioning in patients in the early vs. late stage of bipolar disorder. Acta Psychiatr Scand. 2012.
14. Rosa AR, Reinares M, Amann B, Popovic D, Franco C, Comes M, et al. Six-month functional outcome of a bipolar disorder cohort in the context of a specialized-care program. Bipolar Disord. 2011;13(7-8):679-86.
15. Reinares M, Colom F, Rosa AR, Bonnín CM, Franco C, Solé B, et al. The impact of staging bipolar disorder on treatment outcome of family psychoeducation. J Affect Disord. 2010;123(1-3):81-6.
16. Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry. 2006;188:313-20.
17. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Brietzke E, Vazquez GH, Vieta E, et al. The potential use of biomarkers as an adjunctive tool for staging bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(8):1366-71.
18. Kapczinski F, Dias VV, Kauer-Sant'Anna M, Frey BN, Grassi-Oliveira R, Colom F, et al. Clinical implications of a staging model for bipolar disorders. Expert Rev Neurother. 2009;9(7):957-66.
19. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord. 2007;100(1-3):279-81.
20. Vieta E, Reinares M, Rosa AR. Staging bipolar disorder. Neurotox Res. 2011;19(2):279-85.
21. Berk M, Malhi GS, Hallam K, Gama CS, Dodd S, Andreazza AC, et al. Early intervention in bipolar disorders: clinical, biochemical and neuroimaging imperatives. J Affect Disord. 2009;114(1-3):1-13.
22. Magalhães PVS, Fries GR, Kapczinski F. Peripheral markers and the pathophysiology of bipolar disorder. Rev psiquiatr clín. 2012;39(2):60-7.
23. Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Goncalves CA, et al. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett. 2006;398(3):215-9.
24. de Oliveira GS, Cereser KM, Fernandes BS, Kauer-Sant'Anna M, Fries GR, Stertz L, et al. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J Psychiatr Res. 2009;43(14):1171-4.
25. Machado-Vieira R, Dietrich MO, Leke R, Cereser VH, Zanatto V, Kapczinski F, et al. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. Biol Psychiatry. 2007;61(2):142-4.
26. Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett. 2009;452(2):111-3.
27. Lin PY. State-dependent decrease in levels of brain-derived neurotrophic factor in bipolar disorder: a meta-analytic study. Neurosci Lett. 2009;466(3):139-43.
28. Fernandes BS, Gama CS, Cereser KM, Yatham LN, Fries GR, Colpo G, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011;45(8):995-1004.
29. Kauer-Sant'Anna M, Kapczinski F, Andreazza AC, Bond DJ, Lam RW, Young LT, et al. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int J Neuropsychopharmacol. 2009;12(4):447-58.
30. Yatham LN, Kapczinski F, Andreazza AC, Trevor Young L, Lam RW, Kauer-Sant'anna M. Accelerated age-related decrease in brain-derived neurotrophic factor levels in bipolar disorder. Int J Neuropsychopharmacol. 2009;12(1):137-9.
31. Kauer-Sant'anna M, Yatham LN, Tramontina J, Weyne F, Cereser KM, Gazalle FK, et al. Emotional memory in bipolar disorder. Br J Psychiatry. 2008;192(6):458-63.
32. Frey BN, Valvassori SS, Reus GZ, Martins MR, Petronilho FC, Bardini K, et al. Effects of lithium and valproate on amphetamine-induced oxidative stress generation in an animal model of mania. J Psychiatry Neurosci. 2006;31(5):326-32.
33. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psychiatry. 2009;70(8):1078-90.
34. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J Affect Disord. 2009;116(3):214-7.

35. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord. 2007;104(1-3):91-5.
36. Brietzke E, Kauer-Sant'Anna M, Teixeira AL, Kapczinski F. Abnormalities in serum chemokine levels in euthymic patients with bipolar disorder. Brain Behav Immun. 2009;23(8):1079-82.
37. Kunz M, Ceresér KM, Goi PD, Fries GR, Teixeira AL, Fernandes BS, et al. Serum levels of IL-6, IL-10 and TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev Bras Psiquiatr. 2011;33(3):268-74.
38. Brietzke E, Kapczinski F. TNF-alpha as a molecular target in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(6):1355-61.
39. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008;63(8):801-8.
40. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord. 2008;111(2-3):135-44.
41. Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Nardin P, et al. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007;41(6):523-9.
42. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, et al. A systemic toxicity index developed to assess peripheral changes in mood episodes. Mol Psychiatry. 2010;15(8):784-6.
43. Magalhães PV, Jansen K, Pinheiro RT, Colpo GD, da Motta LL, Klamt F, et al. Peripheral oxidative damage in early-stage mood disorders: a nested population-based case-control study. Int J Neuropsychopharmacol. 2011:1-8.
44. Andreazza AC, Frey BN, Erdtmann B, Salvador M, Rombaldi F, Santin A, et al. DNA damage in bipolar disorder. Psychiatry Res. 2007;153(1):27-32.
45. Rybakowski JK, Wykretowicz A, Heymann-Szlachcinska A, Wysocki H. Impairment of endothelial function in unipolar and bipolar depression. Biol Psychiatry. 2006;60(8):889-91.
46. Kapczinski F, Frey BN, Andreazza AC, Kauer-Sant'Anna M, Cunha AB, Post RM. Increased oxidative stress as a mechanism for decreased BDNF levels in acute manic episodes. Rev Bras Psiquiatr. 2008;30(3):243-5.
47. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, et al. Peripheral biomarkers and illness activity in bipolar disorder. J Psychiatr Res. 2011;45(2):156-61.
48. Magalhães PV, Jansen K, Pinheiro RT, Klamt F, Teixeira AL, da Silva RA, et al. Systemic toxicity in early-stage mood disorders. J Psychiatr Res. 2011;45(10):1407-9.
49. Fornito A, Malhi GS, Lagopoulos J, Ivanovski B, Wood SJ, Saling MM, et al. Anatomical abnormalities of the anterior cingulate and paracingulate cortex in patients with bipolar I disorder. Psychiatry Res. 2008;162(2):123-32.
50. Konarski JZ, McIntyre RS, Kennedy SH, Rafi-Tari S, Soczynska JK, Ketter TA. Volumetric neuroimaging investigations in mood disorders: bipolar disorder versus major depressive disorder. Bipolar Disord. 2008;10(1):1-37.
51. Hallahan B, Newell J, Soares JC, Brambilla P, Strakowski SM, Fleck DE, et al. Structural magnetic resonance imaging in bipolar disorder: an international collaborative mega-analysis of individual adult patient data. Biol Psychiatry. 2011;69(4):326-35.
52. Martinez-Arán A, Vieta E, Colom F, Reinares M, Benabarre A, Torrent C, et al. Neuropsychological performance in depressed and euthymic bipolar patients. Neuropsychobiology. 2002;46 Suppl 1:16-21.
53. Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry. 2004;161(2):262-70.
54. Martínez-Arán A, Vieta E, Colom F, Torrent C, Reinares M, Goikolea JM, et al. Do cognitive complaints in euthymic bipolar patients reflect objective cognitive impairment? Psychother Psychosom. 2005;74(5):295-302.
55. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord. 2006;93(1-3):105-15.
56. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord. 2006;8(2):103-16.
57. Martinez-Arán A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, et al. Functional outcome in bipolar disorder: the role of clinical and cognitive factors. Bipolar Disord. 2007;9(1-2):103-13.
58. Torrent C, Martinez-Aran A, Daban C, Sanchez-Moreno J, Comes M, Goikolea JM, et al. Cognitive impairment in bipolar II disorder. Br J Psychiatry. 2006;189:254-9.
59. Üstun TB. The global burden of mental disorders. Am J Public Health. 1999;89(9):1315-8.
60. Rosa AR, Franco C, Martínez-Aran A, Sánchez-Moreno J, Reinares M, Salamero M, et al. Functional impairment in patients with remitted bipolar disorder. Psychother Psychosom. 2008;77(6):390-2.
61. Swann AC, Bowden CL, Calabrese JR, Dilsaver SC, Morris DD. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. Am J Psychiatry. 1999;156:1264-6.
62. Maj M. The impact of lithium prophylaxis on the course of bipolar disorder: a review of the research evidence. Bipolar Disord. 2000; 2:93-101.
63. Berk M, Brnabic A, Dodd S, Kelin K, Tohen M, Malhi GS, et al. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord. 2011;13(1):87-98.
64. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Goncalves CA, et al. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. J Psychiatry Neurosci. 2009;34(4):263-71.
65. Lewandowski KE, Cohen BM, Ongur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. Psychol Med. 2011;41(2):225-41.